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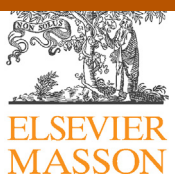

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GUIDELINES

Diagnosis and treatment of iron deficiency in patients with heart failure: Expert position paper from French cardiologists

Diagnostic et traitement de la carence martiale chez les patients insuffisants cardiaques : le point de vue d'experts cardiologues français

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KEYWORDS
Heart failure;
Iron deficiency;
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Summary The prevalence of iron deficiency is high — even in the absence of anaemia — in patients with chronic heart failure (HF). Although iron deficiency is easily diagnosed with two biomarkers (serum ferritin and transferrin saturation), it is underdiagnosed in patients with HF. Iron is not only necessary for red blood cells, but also for cells in tissues with high-energy

Abbreviations: ESC, European Society of Cardiology; HF, Heart Failure; LVEF, Left Ventricular Ejection Fraction; NT-proBNP, N-Terminal Fragment of pro-B-type Natriuretic Peptide; NYHA, New York Heart Association; pVO_2, Peak Oxygen Uptake; TIBC, Total Iron Binding Capacity; TSA, Ttransferrin Saturation.

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Serum ferritin;
Transferrin saturation

demands (heart, muscle, brain). Even before the onset of anaemia, HF patients with iron deficiency have decreased physical and cognitive performances and a poorer quality of life. Moreover, iron deficiency is a risk factor, independent of anaemia, of unfavourable outcome (death or heart transplantation) in patients with chronic HF. Several randomized controlled studies have shown improvement in exercise capacity, New York Heart Association functional class and quality of life after correction of iron deficiency. The results of these clinical trials, which are supported by European guidelines, suggest considering iron deficiency in HF as a possible therapeutic target.

MOTS CLÉS
Insuffisance cardiaque ;
Carence martiale ;
Fer injectable ;
Ferritine sérique ;
Coefficient de saturation de la transferrine

Résumé La prévalence de la carence martiale— même en l'absence d'anémie —est élevée chez les patients présentant une insuffisance cardiaque chronique. Bien que la carence martiale soit facilement diagnostiquée avec deux paramètres biologiques (ferritine sérique et coefficient de saturation de la transferrine), elle reste toutefois sous-diagnostiquée chez ces patients. Le fer est nécessaire, non seulement aux cellules de la lignée érythrocytaire, mais également aux tissus ayant une consommation énergétique importante (cœur, muscles, cerveau). Bien avant que l'anémie ferriprive soit constituée, les patients avec une carence martiale ont des performances physiques et cognitives diminuées et une qualité de vie dégradée. Chez les patients insuffisants cardiaques, la carence martiale est un facteur de risque (décès, transplantation cardiaque), indépendant de l'anémie. Plusieurs essais randomisés contrôlés ont montré l'amélioration des performances physiques, de la classe fonctionnelle NYHA, et de la qualité de vie après correction de la carence martiale. Les résultats de ces essais cliniques, soutenus par des recommandations européennes, suggèrent de considérer la carence martiale des patients insuffisants cardiaques comme une cible thérapeutique potentielle.

Background

This position paper reports data on iron deficiency in patients with heart failure (HF), which are based on: a review and analysis of recent articles on iron metabolism and HF; national and international guidelines for the management of HF, and iron deficiency diagnosis and treatment; and the experience of the authors with iron deficiency in HF patients.

In recent years, iron deficiency has emerged as a newly recognized co-morbidity of chronic HF. Independently of anaemia, iron deficiency occurs frequently in HF patients, contributing to cardiac and peripheral muscle dysfunction, and is a strong predictor of poor clinical outcome [1—3]. Recent controlled randomized studies have shown that iron treatment in chronic HF has favourable effects on exercise capacity, New York Heart Association (NYHA) functional class, left ventricular ejection fraction (LVEF) and quality of life [4—8]. Despite this, the diagnosis and management of HF patients with iron deficiency remains largely unrecognized in the cardiologist community. However, diagnostic tools and treatments already exist are relatively inexpensive and may lead to important health benefits for HF patients.

This document is intended for use by cardiologists, and the recommendations herein propose preferred approaches for the diagnosis and treatment of iron deficiency in HF. Recommendations from position papers are not considered to have the prominence of practice guidelines. Nevertheless, based on the latest literature, this position paper should facilitate and improve patient care by presenting the best practices in this emerging area.

Recent perspectives on iron deficiency physiopathology

Iron is necessary not only in the haem of haemoglobin for oxygen transport, but also as a cofactor for several enzymes. For example, iron ions play central roles in the mitochondrial respiratory chain and in tissue oxygen storage in myoglobin [9]. Therefore, iron is necessary in cells that require sustained adenosine triphosphate synthesis, such as skeletal myocytes and cardiomyocytes, in addition to cells of the erythropoietic lineage [10,11].

In healthy individuals, approximately two-thirds of body iron is contained in the haemoglobin of mature erythrocytes (1800 mg) and precursors of the erythropoietic lineage (300 mg) [12]. Iron is also stored in liver parenchymal cells (1000 mg), with 10—15% found in myoglobin and different enzymes. About 10 mg of iron are ingested daily, although only 1—2 mg are absorbed by duodenal cells. Approximately 3 mg of iron (< 0.2% of total iron) are bound to serum transferrin. Iron is also recycled from senescent red blood cells (600 mg) in macrophages of the reticuloendothelial system (liver, spleen, bone marrow). Thus, iron is continuously exchanged between senescent red blood cells and bone marrow (daily recycling of 20—25 mg of iron).

Iron metabolism and regulation have been revisited recently, and classical clinical findings, such as iron sequestration during chronic inflammation, are now elucidated at the molecular level [13,14]. The proteins ferritin and transferrin play key roles in the storage and transport of iron. Ferritin stores iron in tissues and, in practice, serum ferritin

is the first indicator of iron stores. Absolute iron deficiency is the result of low serum ferritin levels, reflecting insufficient tissue stores of iron as a consequence of chronic blood loss (e.g. gastrointestinal bleeding due to aspirin or oral anticoagulants) or inadequate iron intake (e.g. elderly, malnutrition, malabsorption).

Transferrin carries iron in plasma and extracellular fluids. The iron-transferrin complex is fixed by the transferrin receptor on the membrane of iron-requiring cells, followed by internalization of transferrin to acquire intracellular iron. In chronic inflammation, iron stores are sufficient, but iron cannot be mobilized from the tissue stores to the circulating pool; this status defines functional iron deficiency. The ferritin level may be within normal or high ranges. In this case, the transferrin saturation (TSAT) level should be measured, with a decrease of TSAT indicating a failure to deliver iron to cells and suggesting a diagnosis of functional iron deficiency. The level of circulating iron decreases due to: iron retention in macrophages of the reticuloendothelial system; and decreased intestinal absorption of iron [15]. Retention of iron in macrophages and decreased absorption of iron by intestinal cells are related to increased synthesis of hepcidin, a newly discovered peptide produced by the liver that plays a central role in iron metabolism regulation [16]. There is an important therapeutic consequence of this mechanism: correction of iron deficiency is more rapid and more efficient via the intravenous route compared with oral administration because the intestinal barrier is bypassed and iron sequestration is overcome [17]. These mechanisms have important implications in inflammatory diseases or when malabsorption is present, including HF, which is often associated with mild inflammation and with malabsorption in case of peritoneal oedema.

Clinical consequences of iron deficiency

The best known consequence of iron deficiency is anaemia; however, anaemia is the result of advanced-stage iron deficiency. Iron deficiency has important clinical consequences before the onset of anaemia [9], with many chronic diseases worsening if iron deficiency occurs, even in the absence of anaemia [10,14]. In a systematic literature review of animal and human studies, the causal relationship between iron deficiency and decreased physical capacity/work was clearly established, even in patients without anaemia. This impairment of exercise capacity is related to mitochondrial dysfunction and a decrease of oxygen storage in myoglobin, resulting in decreased energetic efficiency [9,18]. The consequences of iron deficiency on cognitive performances, emotions and behaviour have also been demonstrated [19,20]. Of note, exercise performance and cognition in patients with iron deficiency were improved after iron supplementation [19—22].

Other experimental or clinical studies have shown more specifically the consequences of iron deficiency on cardiac muscle. In an animal model, chronic iron deficiency resulted in structural abnormalities, with increased size and weight of the heart [18]. A recent study reported that iron content and transferrin receptor expression were decreased in cardiomyocytes from HF patients [23]. In a prospective study in patients with chronic HF, patients who were non-anaemic and iron deficient had a 2-fold greater risk of death than anaemic iron-replete patients [3]. Iron deficiency was shown to be a strong predictor, independent of anaemia, of unfavourable outcome (e.g. death or heart transplantation) in patients with systolic chronic HF [1]. Iron deficiency was also an independent predictor of mortality in chronic HF patients; disease severity and the level of the N-terminal fragment of pro-B-type natriuretic peptide (NT-proBNP) were associated with the degree of iron deficiency [2].

Prevalence of iron deficiency in patients with heart failure

Iron deficiency occurs frequently (30—50%) in patients with chronic HF, with or without anaemia [2,24—29]. In a cohort study of 955 patients with HF, iron deficiency was reported in 43% of anaemic patients and 15% of non-anaemic patients [25]. In a separate study, iron deficiency anaemia was diagnosed by bone marrow aspiration in 73% of 37 patients with advanced HF [27]. More recently, iron deficiency was diagnosed in 37% of 546 patients with HF (including 32% of patients without anaemia) [1]. In 157 patients with chronic HF, functional iron deficiency was diagnosed in 43% of patients, although there was apparently no deficiency of iron stores [3]. In an international study, the prevalence of iron deficiency was 50% in 1506 patients with chronic HF (including 46% of patients without anaemia) [2]. A recent cohort study in patients hospitalized for decompensation of HF reported iron deficiency in 69% of men and 75% of women (57% and 79% in non-anaemic patients, respectively) [30].

Diagnosis and initial evaluation of iron deficiency in heart failure

Biological marker of iron stores: serum ferritin

Values of serum iron have substantial variation between HF patients, in addition to nycthemeral variations. Therefore, measurement of serum iron is no longer recommended for the diagnosis of iron deficiency. Instead, the level of serum ferritin, which stores iron in tissues in a non-toxic form, is used as a marker of iron deficiency, because serum ferritin levels correlate with total body iron stores.

In the general population, reference ranges of serum ferritin are within 15—300 μg/L [31]. Iron deficiency is considered to be certain for serum ferritin < 15 μg/L [32]. However, ferritin is also an acute phase inflammatory protein and, as such, its concentration increases in chronic HF and other chronic diseases due to inflammation processes. Therefore, in patients with chronic diseases, increased ferritin levels do not always reflect high iron stores, and the customary thresholds that indicate iron deficiency may not apply. Nanas et al. showed that serum ferritin, at a cut-off at 17 μg/L, minimized the incidence of iron deficiency compared with the gold standard, which is bone marrow aspiration with specific staining of iron (Perls' Prussian blue staining of ferric irons in tissue, mostly within ferritin) [27]. Coenen et al. showed that, in patients who

had anaemia associated with chronic disease and ferritin concentrations < 70 μg/L, iron deficiency, as determined by bone marrow iron stain, was always present [33]. One method to account for the increase in ferritin values caused by inflammation is to raise the cut-off that defines iron deficiency [32]. Current thresholds for serum ferritin are derived largely from the clinical literature, specifically from studies examining the highest ferritin concentration among patients with microcytic iron deficiency anaemia who had no stainable iron in the bone marrow (or, alternatively, who showed a therapeutic response to iron) [32].

Biological marker of iron delivery to cells: transferrin saturation

Transferrin is the specific transport protein for iron in plasma; it delivers iron to cells via the transferrin receptor. Serum transferrin can be measured directly by a specific immunological assay or indirectly by determining the total iron binding capacity (TIBC), as transferrin is the primary iron-transport protein. Because transferrin concentration is sensitive to several factors, it is not used in practice to determine iron deficiency [32].

TSAT is a frequently used marker of iron delivery to cells that assesses the fraction of sites on transferrin that are actually occupied by iron ions; it is calculated by dividing the serum iron concentration by the serum transferrin concentration (or by the concentration of the substitute TIBC). TSAT represents the amount of iron available to erythroblasts and other iron-requiring cells, and it is not (or slightly) affected by inflammation in chronic diseases; a TSAT < 20% is insufficient to meet normal requirements for erythropoiesis [34].

Available guidelines for the diagnosis of iron deficiency

In the 2012 guidelines of the European Society of Cardiology (ESC) for the diagnosis and treatment of HF [34], the evaluation of iron status is recommended in all ambulatory patients suspected of having HF. In these guidelines, iron deficiency is defined in accordance with the selection criteria for iron treatment in the study by Anker et al. [4]: ferritin < 100 μg/L; or ferritin 100—299 μg/L plus TSAT < 20% (Table 1). Use of this pragmatic definition allows the identification of patients with chronic HF who could benefit from iron replenishment.

According to the French Health Agency (Haute Autorité de santé), serum ferritin is recommended for the initial diagnosis of iron deficiency (Table 1). Measurement of transferrin saturation is prescribed in cases of inflammation or chronic renal insufficiency, or in cases of normal or increased serum ferritin levels with suspicion of iron deficiency [35]. Measurement of serum iron should not be used for diagnosis, because it exhibits large nycthemeral variations and therefore is less informative than serum ferritin [35]. Of note, these recommendations are general and are not specific to HF patients; no cut-off is specified for serum ferritin in the inflammatory context.

In the 2013 American College of Cardiology Foundation and American Heart Association guidelines for the management of HF, there are no specific recommendations for the diagnosis or treatment of iron deficiency [36].

Expert recommendations

Recent clinical studies are in favour of a systematic assessment of iron status in ambulatory HF patients receiving optimal medical therapy and in patients hospitalized for acute decompensation of chronic HF.

Only serum ferritin and TSAT are useful for iron deficiency diagnosis (do not determine serum iron).

Serum ferritin < 100 μg/L defines absolute iron deficiency; serum ferritin 100—299 μg/L with TSAT < 20% defines functional iron deficiency.

If the first assessment of iron status is normal, the interval between the next iron tests should be 6 months for NYHA functional classes III—IV and 1 year for NYHA functional classes I—II.

Iron administration in patients with heart failure

Recent clinical studies

Five studies have assessed iron supplementation in chronic HF, including three randomized, placebo-controlled studies [4—8]. These studies are summarized in Table 2. Toblli et al. described a prospective randomized double-blind placebo-controlled trial that included 40 chronic HF patients with LVEF ≤ 35%, anaemia (haemoglobin < 12.5 g/dL in men and < 11.5 g/dL in women), iron deficiency (serum ferritin < 100 μg/L and/or transferrin saturation < 20%), and mild renal insufficiency (creatinine clearance ≤ 90 mL/min) [7]. Intravenous iron sucrose significantly increased haemoglobin and iron variables; NT-proBNP ($P < 0.01$) and C-reactive protein ($P < 0.01$) were significantly decreased. NYHA functional class, Minnesota Living with Heart Failure questionnaire score, 6-minute walk distance and LVEF were significantly improved in the iron sucrose group ($P < 0.01$ for all).

The Ferric Iron Sucrose in Heart Failure (FERRIC-HF) study was a randomized controlled observer-blinded trial of 35 patients with chronic HF (NYHA functional class II—III) and iron deficiency who received intravenous iron sucrose or placebo [6]. Compared with the placebo group, there was no significant increase in absolute peak oxygen uptake (pVO_2) in the iron group (primary endpoint; 95% confidence interval—12—205 mL/min; $P = 0.08$); in contrast, pVO_2 adjusted to body weight was significantly increased (95% confidence interval 0.5—4 mL/kg/min; $P = 0.01$).

Ferinject assessment in patients with iron deficiency and chronic heart failure (FAIR-HF) was a multicentre prospective double-blind randomized placebo-controlled study of 459 patients with NYHA functional class II—III and iron deficiency (with or without anaemia), defined as ferritin level < 100 μg/L or ferritin level 100—299 μg/L with transferrin saturation < 20% [4,37]. In the carboxymaltose iron group, serum ferritin and haemoglobin levels were significantly increased and were associated with significant functional improvement in the patient self-reported global assessment (50% of patients in the iron group versus 28% in the placebo

Table 1 Guidelines and recommendations for the diagnosis and treatment of iron deficiency.

	European Society of Cardiology 2012: general guidelines for HF [34]	French Health Agency (Haute Autorité de santé) 2011: general guidelines for iron deficiency [35]	Present position paper: Expert opinion specific to iron deficiency in HF
Diagnosis of iron deficiency	Iron deficiency is a co-morbidity of HF that must be detected	For suspicion of iron deficiency, serum ferritin is the first-line iron variable (no other biological variable is necessary)	Iron deficiency should be systematically assessed in all HF patients
	Iron deficiency is defined by the selection criteria for chronic HF patients eligible for iron treatment in the study by Anker et al. [4]: ferritin < 100 μg/L or ferritin 100—299 μg/L and TSAT < 20%	In the case of inflammation, chronic renal insufficiency or non-contributory result of serum ferritin (normal or elevated value with strong suspicion of iron deficiency), serum iron associated with transferrin (for calculation of TSAT) can help in the diagnosis No indication for diagnosis by serum iron alone or in addition to serum ferritin	Iron deficiency is defined by: ferritin < 100 μg/L (absolute iron deficiency) or serum ferritin 100—299 μg/L and TSAT < 20% (functional iron deficiency)
Treatment of iron deficiency	Iron therapy may be considered as a treatment for chronic HF patients (correction of iron deficiency in the study by Anker et al. [4] used intravenous iron)	No specific recommendations for the treatment of iron deficiency in HF patients	For all patients with chronic HF or hospitalized for acute decompensation of chronic HF with biological evidence of iron insufficiency, iron supplementation should be considered Oral iron supplementation is the first-line treatment, with assessment of efficacy after 3 months
	The effects of treating iron deficiency in HF with preservation of ejection fraction and the long-term safety of iron therapy in HF are unknown		Intravenous iron (iron sucrose, iron dextran, ferric carboxymaltose) should be administered if oral iron is inefficient or poorly tolerated, or if a rapid increase in iron stores is needed (e.g. in symptomatic anaemia) The efficacy of intravenous iron should be assessed after 3 months

HF: heart failure; TSAT: transferrin saturation.

group; $P < 0.001$). NYHA functional class also improved, with 47% of patients in the iron group and 30% in the placebo group in class I—II ($P < 0.001$). Additionally, health-related quality of life assessments and 6-minute walk distance were significantly improved in the iron group ($P < 0.001$ for all comparisons). Of note, similar results were observed regardless of anaemia status, although haemoglobin level in the non-anaemic subgroup did not increase after iron supplementation.

Ongoing clinical studies

Ongoing clinical trials in chronic HF are evaluating the direct impact of iron supplementation on daily symptoms

Table 2 Clinical trials with intravenous iron in patients with heart failure.

Authors	Patients (*n*)	Iron and anaemia status	Disease severity	Iron treatment (mean dosage)	Follow-up	Study results
Uncontrolled studies						
Bolger et al. (2006) [5]	16	Anaemia	NYHA class II–III	Iron sucrose (950 ± 137 mg)	92 days	Improvement in NYHA functional class ($P < 0.02$), MLHF questionnaire score ($P = 0.002$) and 6-minute walk distance
Usmanov et al. (2008) [8]	32	Anaemia with iron deficiency	NYHA class III–IV	Iron sucrose	26 weeks	Improvement in cardiac remodelling and NYHA functional class in patients with baseline NYHA class III ($P < 0.01$)
Randomized placebo-controlled studies						
Toblli et al. (2007) [7]	40	Iron deficiency and anaemia	NYHA class II–IV; ejection fraction ≤ 35%	Iron sucrose	6 months	Reduction in NT-proBNP ($P < 0.01$) and CRP ($P < 0.01$); improvement in LVEF, NYHA functional class, exercise capacity, renal function and quality of life (all $P < 0.01$)
Okonko et al. (2008) (FERRIC-HF study) [6]	35	Iron deficiency with and without anaemia	NYHA class II–III	Iron sucrose (928 ± 219 mg)	18 weeks	Increase in pVO_2/kg ($P = 0.01$); improvement in NYHA functional class ($P = 0.007$) and patient global assessment ($P = 0.002$)
Anker et al. (2009) (FAIR-HF study) [4]	459	Iron deficiency with or without anaemia	NYHA class II–III	Ferric carboxymaltose (1850 ± 433 mg)	24 weeks	Improvement in patient global assessment and NYHA functional class (primary criteria; $P < 0.001$); improvement in 6-minute walk distance and quality of life ($P < 0.001$); similar effect in patients with or without anaemia

CRP: C-reactive protein; HF: heart failure; LVEF: left ventricular ejection fraction; MLHF: minnesota living with heart failure; NT-proBNP: N-terminal fragment of pro-B-type natriuretic peptide; NYHA: New York Heart Association; pVO_2: peak oxygen uptake.

and exercise capacity. The Iron Supplementation in Heart Failure Patients with Anaemia study (IRON-HF; ClinicalTrials.gov identifier, NCT00386126; estimated enrolment, $n = 117$) is evaluating the impact of supplementation with intravenous or oral iron on changes in pVO_2, as measured with ergospirometry [38]. A study from the Anaemia Working Group Romania will assess the efficiency of intravenous iron in mild to moderate anaemia associated with chronic

Table 3 Dosage and administration of the different pharmacological forms of intravenous iron.

Intravenous iron complexes	Dosage	Administration
Iron carboxymaltose (Ferinject®)	Intravenous infusion at 15 mg/kg (for a total ≤ 1000 mg) once/week	Intravenous infusion in NaCl 0.9% with iron concentration > 2 mg/mL From 100 to < 200 mg: 50 mL of 0.9% NaCl From 200 to < 500 mg: 100 mL of 0.9% NaCl (in ≥ 6 minutes) From 500—1000 mg: 250 mL of 0.9% NaCl (in ≥ 15 minutes)
	Bolus intravenous injection of 200 mg/day (≤ 3 injections/week)	Bolus intravenous injection at a maximal dose of 200 mg
Iron-hydroxide sucrose (Venofer® and similar)	100—300 mg/injection; 1—3 injections/week with a 48-hour interval between each injection	Slow intravenous infusion (3.5 mL/min) with a duration ≥ 1.5 hours; one ampoule diluted in ≤ 100 mL of 0.9% NaCl
Iron-hydroxide dextran (Ferrisat®)[a]	100—200 mg/injection (not exceeding 20 mg/kg); 1—3 injections/week with a 48—hour interval between each injection	Intravenous infusion of 1 or 2 ampoules (100 or 200 mg) in 100 mL of 0.9% NaCl or 5% glucose
		Slow intravenous injection of 100—200 mg of iron (0.2 mL/min), preferably diluted in 10—20 mL of 0.9% NaCl or 5% glucose

NaCl: sodium chloride.
[a] The French Ministry of Health has stopped Ferrisat® reimbursement because of allergic adverse events such as anaphylactic shocks.

HF (NYHA functional class III) and concomitant moderate chronic kidney disease (NCT00384657; $n = 200$) based on the ejection fraction value. The aim of the Effect of Ferric Carboxymaltose on Exercise Capacity in Patients With Iron Deficiency and Chronic Heart Failure study (EFFECT-HF; NCT01394562; $n = 160$) is to assess the impact of intravenous ferric carboxymaltose on pVO_2, exercise capacity, symptoms and quality of life in patients with chronic HF and iron deficiency. The Comparison of Ferric Carboxymaltose With Placebo in Patients With Chronic Heart Failure and Iron Deficiency study (CONFIRM-HF; NCT01453608; $n = 300$) is also evaluating the effect of iron repletion with intravenous ferric carboxymaltose on exercise capacity in patients with chronic HF and iron deficiency.

Available guidelines for iron supplementation in heart failure

On the basis of the study by Anker et al. [4,37], which included chronic HF patients, the ESC 2012 guidelines for acute and chronic HF state that iron therapy may be considered as a treatment for these patients (Table 1) [34]. In these guidelines, only the intravenous route is considered; there are indeed some arguments in favour of the intravenous route over the oral route (Table 3). Retention of iron in macrophages and decreased absorption of iron by intestinal cells are consequences of inflammation, which occurs frequently in chronic diseases [16]. Intestinal morphology, permeability and absorption are modified in chronic HF patients [39]. With intravenous iron administration, correction of iron deficiency is more rapid and efficient because the intestinal barrier is bypassed and iron sequestration is overcome [17].

Nevertheless, other considerations have to be taken into consideration. First, the intravenous and oral routes for iron supplementation have not been formally compared in a clinical trial in chronic HF. Second, according to market authorizations of the different intravenous iron compounds (iron sucrose, dextran iron, ferric carboxymaltose), oral iron is considered the first-line treatment; the intravenous route is to be considered if oral treatment is inefficient or cannot be used (e.g. intolerance or adverse events). Although the risk of serious hypersensitivity reactions is low, intravenous iron must be administered and monitored in an hospital.

Expert recommendations

Recent clinical studies suggest that iron supplementation should be considered for patients with chronic HF receiving optimal medical therapy or hospitalized for acute decompensation of chronic HF with biological evidence of iron insufficiency.

Oral iron supplementation should be used for first-line treatment of iron deficiency, with assessment of efficacy after 3 months (serum ferritin ≥ 100 μg/L and TSAT ≥ 20%).

Intravenous iron (iron sucrose, iron dextran, ferric carboxymaltose) should be administered if oral iron is inefficient or poorly tolerated, or if a rapid increase in iron stores is needed (e.g. in symptomatic anaemia).

The efficacy of intravenous iron should be assessed after 3 months (serum ferritin ≥ 100 μg/L and TSAT ≥ 20%).

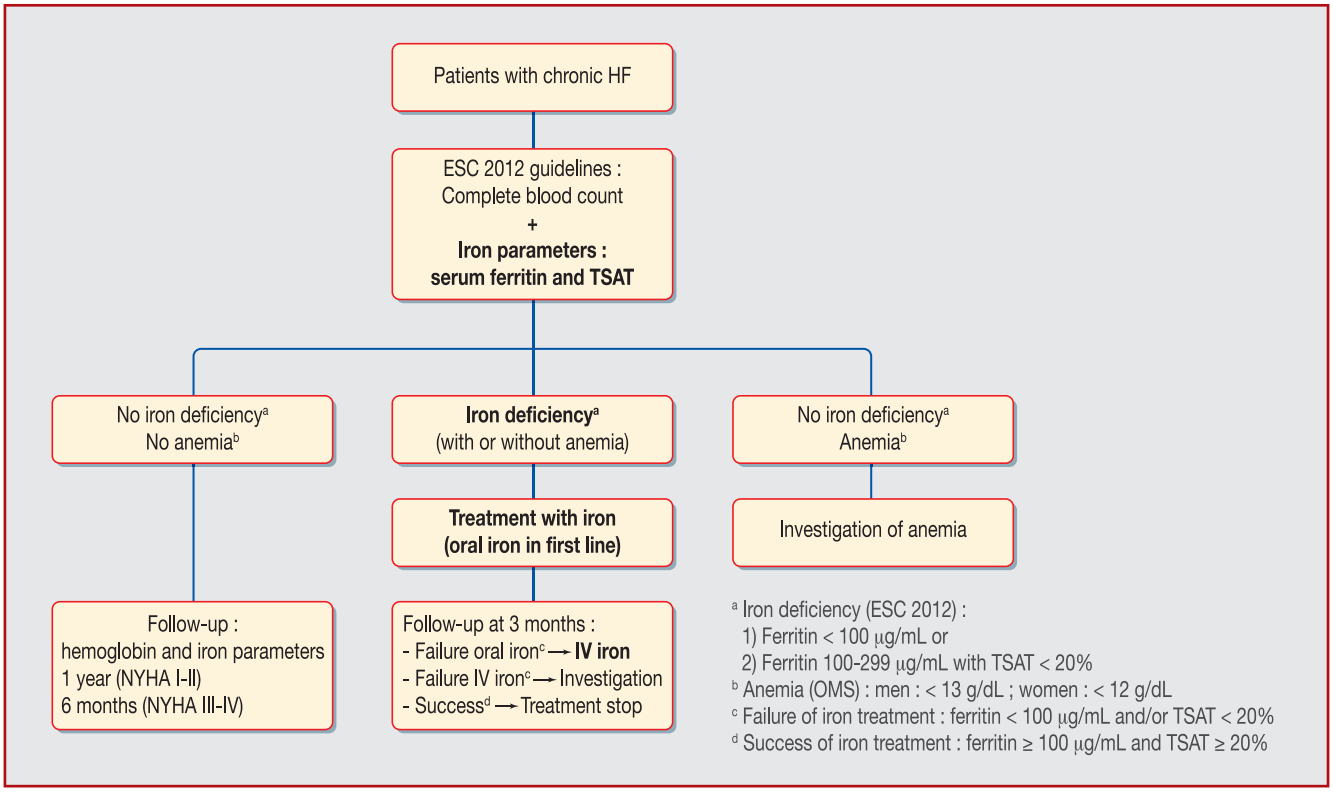

Figure 1. Assessment of iron variables and treatment of iron deficiency in chronic heart failure. ESC: European Society of Cardiology; HF: heart failure; IV: intravenous; NYHA: New York Heart Association; OMS: Organización Mundial de la Salud (World Health Organization); TSAT: transferrin saturation.

Conclusion

The high prevalence of iron deficiency in patients with chronic HF, even in the absence of anaemia, is now well-established. Despite this, iron deficiency is underdiagnosed in HF patients, although it is recognized as a predictor of outcome in chronic HF. Cardiologists should be aware of the consequences of iron deficiency in these patients, and should routinely assess iron status with measurement of serum ferritin and TSAT (Fig. 1). Several studies have shown improvement in exercise capacity, NYHA functional class and quality of life after correction of iron deficiency. The results of clinical trials should encourage cardiologists to consider iron deficiency as a therapeutic target in HF.

Disclosure of interest

C. Leclercq, M. Galinier, P. de Groote and T. Damy have received honoraria from Vifor Pharma as expert board members. A. Cohen-Solal has received honoraria from Vifor Pharma as an expert board member and as a participant in a clinical trial. R. Isnard has received speaker's honoraria from Vifor France. A. Mebazza has received speaker's honoraria from Alere, Bayer, Edwards Life Sciences, The Medicines Company, Novartis, Orion, Servier, Thermo Fisher and Vifor Pharma, and has received fees as a member of an advisory board and/or Steering Committee from Bayer, Cardiorentis, The Medicines Company and Critical Diagnostics.

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